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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,429	01/22/2002	Ekambar R. Kandimalla	47508-580 (HYZ-027CIP)	7279

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,429	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *6,7,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-13 and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-08-03; 8-07-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-5, 8-13, and 16-19 in the Paper filed 10/01/2003 is acknowledged. The traversal is on the ground(s) that the compositions of Group I are so closely related to their method of use as claimed in Group II (claims 6-7 and 14-15) that a search for both subject matters would not represent an undue burden in this case. This is not found persuasive because the examiner has previously established in the prior Office Action that the invention according to Group I is patentably distinct from the invention of Group II. As stated previously, the invention of Group I is classified in 536/24.5, and the invention of Group II is classified in 435/375, according to MPEP § 803, "[F]or purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02."

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 6-7 and 14-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Paper filed 10/01/03.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claim 18 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 15-22 of U.S. Patent No. 6,372,427 B1. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claim(s) 18-19 of the instant application are generic to all that is recited in claim(s) 1-7 and 15-22 of U.S. Patent No. 6,372,427. That is, claim(s) 1-7 and 15-22 of U.S. Patent No. 6,372,427 falls entirely within the scope of claim(s) 18-19 or, in other words, claim(s) 18 is anticipated by claim(s) 1-7 and 15-22 of U.S. Patent No. 6,372,427. Specifically, the claims of the instant application, claim 18 of the instant application is drawn to a formulation comprising at least two cooperative oligonucleotides comprising a dimerization

domain, and complementary to non-overlapping regions of a target nucleic acid being separated by 0 to 3 base. Similarly, claims 1-7 of the issued patent are drawn to a composition comprising at least two synthetic cooperative oligonucleotides comprising a dimerization domain, and complementary to a tandem, non-overlapping regions of a target nucleic acid being separated by 0 to 1 base. It is clear that invention according to issued claims 1-7 is encompassed by instant claim 18 which encompasses wherein the oligonucleotides are complementary to tandem non-overlapping regions of a target nucleic acid being separated by 0 to 3 bases, 0 to 3 bases encompasses the 0 to 1 base separation between the non-overlapping regions of the target nucleic acid.

Claim 19 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 15-22 of U.S. Patent No. 6,372,427 B1. Instant claim 19 is drawn to a pharmaceutical composition comprising a duplex structure comprising a first and a second synthetic oligonucleotide, wherein each oligonucleotide comprises a region complementary to a tandem, non-overlapping region of a target nucleic acid, the tandem, non-overlapping regions of the target nucleic acid being separated by 0-1 base, the target nucleic acid being an mRNA, a single-stranded viral DNA, or a single-stranded viral RNA, and the first oligonucleotide having a terminal dimerization domain of the second oligonucleotide when the first and second oligonucleotides are hybridized to the target nucleic acid. Claim 19 differs from issued claim 1 because it is drawn to a pharmaceutical composition comprising a duplex structure comprising a first and a second synthetic oligonucleotide, however issued claim 1 broader in scope than instant claim 19 since claim 1 is broadly drawn to a composition, not necessarily a pharmaceutical composition. Additionally, claim 1 is broadly

drawn to a composition comprising at least two synthetic oligonucleotides, therefore the scope of claim 1 may encompass more than two synthetic oligonucleotides, however instant claim 19 is limited to a composition comprising a duplex structure comprising a first and second synthetic oligonucleotide. Instant claim 19 is an obvious variation of the invention set forth in issued claim 1 because the scope of claim 19 is fully encompassed by the scope of issued claim 1. Additionally, issued claim 1 and instant claim 19 are directed to the same inventive concept, however they differ in scope, and are patentably indistinct from each other.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-6, 8-13, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gryaznov et al. (US Patent No. 5,571,903) in view of Agrawal et al. (US Patent No. 5,691,316).

7. Gryaznov et al. disclose compositions comprising a from two to five components comprising oligonucleotide moieties (of 4 to 12 monomers in length) that specifically anneal to a target polynucleotide in a contiguous end-to-end fashion, wherein each oligonucleotide are modified to comprise a terminal binding moiety (col. 3, lines 1-30). The terminal binding moieties of Gryaznov et al. confer an increase by at least fifty percent over the melting temperatures of the oligonucleotide moieties alone (col. 4, lines 10-15). The oligonucleotides of Gryaznov et al. may also comprise encompass modified oligonucleotides that comprise

internucleoside linkages that confer nuclease resistance, e.g. phosphorothioate, phosphorodithioate, phosphoramidate, or the like (see col. 5, lines 44-48).

However, Gryaznov et al. does not teach oligonucleotide moieties modified with cyclodextrin or adamantine.

Agrawal et al. disclose oligonucleotide compositions comprising oligonucleotides noncovalently associated with cyclodextrin, or alternatively the oligonucleotide may be covalently linked to adamantine which is non-covalently associated with cyclodextrin (see abstract and col. 2, lines 51-59, and col. 3 lines 37-44). Agrawal et al. teach that uptake of antisense oligonucleotides into cells can be enhanced by noncovalently associating oligonucleotides with a cyclodextrin in a manner as set forth in Agrawal et al. (see col. 2, lines 34-40; and col. 5, lines 11-16).

It would have been obvious at the time the instant invention was made to modify the oligonucleotides of Gryaznov et al. with the cyclodextrin or adamantine / cyclodextrin modifications of Agrawal et al. in the design of the presently claimed invention. One of ordinary skill in the art would have been motivated to make this modification because the cyclodextrin or adamantine/cyclodextrin modifications are known in the prior to increase the cellular uptake of oligonucleotides comprising these modifications and thereby increase the efficacy of their application and reducing the dose required (see Agrawal et al. col. 5, lines 11-17).

Therefore, the invention as a whole would have been *prima facie* obvious over Gryaznov et al. in view of Agrawal et al.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites "[T]he composition of claim 1, wherein at least one of the oligonucleotides is modified." This phrase is vague and indefinite since it is clear that both first and second oligonucleotides of the composition of claim 1 are modified to the extent that they encompass oligonucleotides that are linked to a biding partner. Additionally, claim 3 fails to further limit the scope of claim 1. Therefore based upon this observation the scope of instant claim is uncertain.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the claimed pharmaceutical formulations and compositions *in vitro*, does not reasonably provide enablement for the *in vivo* use of the claimed formulations or compositions for treatment purposes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 16-17 are drawn to pharmaceutical formulations comprising the composition of claim 1, or the structure of claim 8, wherein said composition and structure comprise a first and a second oligonucleotide having a first and a second binding partner, respectively. Claim 18 is drawn to a pharmaceutical composition comprising at least two synthetic cooperative oligonucleotides comprising a dimerization domain, and claim 19 is directed to a pharmaceutical formulation comprising a duplex structure comprising a first and a second synthetic oligonucleotide comprising a dimerization domain.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

The instant claims encompass the pharmaceutical use of the oligonucleotide compositions and formulations of the instant invention for treatment purposes. However, the specification as filed does not enable one skilled in the art to use the claimed pharmaceutical compositions or formulations for treatment purposes *in vivo*. Although applicants show *in vitro* success using the claimed oligonucleotides, several problems have been encountered when attempting to use antisense oligonucleotides *in vivo,* including stability of the oligonucleotide and lack of targeting to the desired cell type.

The quantity of experimentation required to practice the invention as claimed would require determining the structures of the mRNA targets that are associated with a particular condition or disease, for which therapy is sought. Determining the structures of the tandem, non-

overlapping complementary oligonucleotides used in the compositions and formulations of the invention, identifying modes of delivery *in vivo* such that the expression of said mRNA target is inhibited at a significant level and for a sufficient amount of time to produce the desired therapeutic effect. Neither the specification as filed, nor the prior art searched, provides any specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In regards to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance or instruction that would teach one of skill in the art how to successfully practice a therapeutic method to treat a disease or condition associated with the expression of a particular mRNA target, comprising the administering to a patient the oligonucleotide compositions and formulations according to the present invention.

Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (1999), states "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]." Furthermore, Crooke describes a variety of factors that influences the activity of antisense-based compounds. Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. The influence of non-antisense effects, for example phosphorothioate oligonucleotides

tend to bind non-specifically to many proteins, wherein such protein binding influences cellular uptake, distribution, metabolism and excretion of said oligonucleotide. Additionally, non-specific protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions studied (Crooke, 1999; p. 3). Crooke clearly teaches that there is a significant level of factors, which influence the behavior of antisense based, compounds thereby rendering the activity of antisense compounds unpredictable.

Branch (1998) also teach that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNA molecules and their association with cellular proteins can render target sites totally unaccessible *in vivo*. Moreover, Branch states that "[H]owever, their *(antisense molecules and ribozymes)* unpredictability confounds research applications of nucleic acid reagents."

Jen et al. (*Stem Cells,* Vol. 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress

needs to be made. Moreover Jen et al. conclude that "[G]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also concluded that "[A] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (see page 315, last two paragraphs).

It is apparent from Branch, Crooke, and Jen et al. that the art of antisense based therapeutics, at the time of filing, was unpredictable and those highly skilled in the art working towards making antisense therapy more predictable have many obstacles to overcome. Therefore, claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

It is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the behavior of antisense oligonucleotides *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a mRNA target, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single nucleic acid target is inhibited and the desired treatment effects are obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE